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# Phage Therapy for Patients with Bleeding Disorders and Periodontal Diseases

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ABSTRACT

Periodontal diseases are frequently associated with bleeding episodes, particularly in patients with hemophilia, wherein the disease manifests as severe bleeding from the gum tissue. Lack of the factor required for proper blood clotting aggravates this condition. Consequently, a vicious cycle ensues: Periodontal diseases precipitate severe bleeding from soft tissues, leading to the formation of pockets in both soft and hard tissues, tooth mobility, and tooth loss. Concurrently, oral hygiene deteriorates, potentially reaching critically low levels or cessation altogether, fostering the accumulation of pathogenic bacteria within the oral cavity and exacerbating the frequency and severity of bleeding episodes. Phage therapy is a promising alternative and non-invasive treatment modality for such patients.

Keywords: Bacteriophages, bleeding disorder, hemophilia, periodontal disease, phage therapy.

## INTRODUCTION

Periodontal diseases commonly result in gum tissue bleeding and tooth mobility, with increased complexity observed in patients with hemophilia due to heightened bleeding severity stemming from low clotting factor concentrations in the blood. Consequently, individuals with hemophilia often exhibit reduced levels of oral hygiene at home and frequent visits to dental clinics, accompanied by increased factor concentrate intake for bleeding control. However, this self-treatment approach often needs to be revised.

Hemophilia encompasses a spectrum of hereditary disorders characterized by deficiencies in clotting factors, leading to prolonged clotting times and a predisposition to excessive bleeding.[1] Hemophilia is categorized into types A, B, and C, corresponding to deficiencies in factors VIII, IX, and XI. Hemophilia A is the most prevalent X-linked recessive disorder.

In general, the symptoms are internal or external bleeding episodes. People with more severe hemophilia suffer more severe and more frequent bleeds, while people with mild hemophilia usually suffer more minor symptoms except after surgery or severe trauma. In cases of moderate hemophilia, symptoms are variable and manifest along a spectrum between severe and mild forms.[2,3]

Periodontitis, an inflammation of the tooth-supporting tissues, arises from various etiological factors such as bacteria, poor oral hygiene, genetics, environmental factors, and systemic health conditions (e.g., diabetes, cardiovascular diseases, viral infections, digestive disorders). The initial stage of periodontitis, gingivitis, is characterized by gum tissue swelling, plaque accumulation, and severe bleeding. In advanced cases, periodontitis extends to surrounding tissues, including the periodontal ligament and alveolar bone, resulting in significant local or generalized gum and bone recession, tooth mobility, and occlusal trauma.[4]

Periodontitis in individuals with hemophilia follows a more complex course, perpetuating a vicious cycle wherein gingivitis-induced gum tissue bleeding exacerbates due to the underlying hemophilia. Reduced oral hygiene practices further contribute to bacterial accumulation, a primary etiological factor in periodontitis development.

Adequate dental care for individuals with hemophilia necessitates minimal traumatic interventions. While treatment for periodontitis typically involves hygienic procedures or surgery, both interventions can induce bleeding, albeit controllable with factor concentrate administration. Nevertheless, repetitive bleeding remains a common challenge in managing periodontitis in individuals with hemophilia.[5,6]

Bacteriophages, viruses that infect and replicate within bacteria and archaea, are composed of proteins that encapsulate a DNA or RNA genome and may have structures that are either simple or elaborate. Their genomes may encode as few as four genes (e.g., MS2) and as many as hundreds of genes. Phages replicate within the bacterium following the injection of their genome into its cytoplasm.[7,8]

The objective of this study is to propose phage therapy as an alternative non-invasive treatment modality for periodontal disease in individuals with hemophilia.

In our case, all patients received oversight from their hematologist. However, for patients with hemophilia, the sole treatment method comprised an infusion of antihemophilic factor concentrate and tranexamic acid.

Given the objective of our trial to assess the efficacy of phages in reducing bleeding episodes from the oral cavity, administering factor concentrates could confound the results. Therefore, in consultation with the hematologist, factor concentrate infusions were withheld from the patients during the study.

Seven patients with hemophilia and severe periodontitis were selected for inclusion in the study. Bacteriological and phage resistance testing was conducted on all patients by obtaining oral cavity biopsies, revealing no phage resistance among the patient cohort. None of the patients received antihemophilic factor concentrate therapy during the study period.

After four patients were excluded, all participants were provided with PHAGIO® as the sole mouthwash for regular use over four weeks. Standard dental procedures were uniformly applied to all patients, including professional dental hygiene consisting of teeth scaling and polishing, prescription of anti-inflammatory toothpaste and mouthwash, and provision of a medium toothbrush after professional cleaning.

PHAGIO® was exclusively used as the mouthwash for the targeted patients throughout the study period. Each milliliter of the drug contained a mixture of sterile filtrates of bacteria including Streptococcus, Staphylococcus, E. coli, Pseudomonas aeruginosa, and Proteus phagolysates, with a phage titer not less than 1X105.

PHAGIO® comprises virulent phages selected from bacteria (Streptococcus, Staphylococcus, E. coli, Pseudomonas aeruginosa, and Proteus), ensuring the drug's high activity and efficacy. Regardless of the route of administration, bacteriophage preparations are rapidly absorbed into the bloodstream and lymphatic system, facilitating their delivery to the site of infection.

All observed patients were distributed among two groups:

- Group 1: Patients received professional oral cavity cleaning and were treated solely with PHAGIO® at an appropriate dosage (10-20 ml orally once daily for four weeks);
- Group 2: Patients underwent standard professional oral hygiene procedures at the dental office without a PHAGIO® prescription. Their toothbrushes were replaced, and they were provided with anti-inflammatory toothpaste and chlorhexidine-containing mouthwash at appropriate dosages for four weeks.

## CASE 1

The first case involved a 28-year-old patient with severe hemophilia A who presented during a dental visit and reported experiencing spontaneous gum bleeding and increased tooth sensitivity, which had gradually intensified over the past few months. Due to the bleeding episodes, the patient had ceased oral hygiene practices and relied solely on antihemophilic factor concentrates for treatment. Professional cleaning had never been performed.

The examination revealed significant plaque accumulation, halitosis, spontaneous severe gum bleeding, and swelling with hyperemia. Grade 1 mobility was noted in the lower anterior teeth (teeth 3, 3-4, 4).

A bacteriological sample was obtained from the oral cavity to assess phage resistance. An oral cavity examination was conducted, and a periodontal map was generated. Figure 1 depicts the patient's condition before and after treatment with plaque removal using scaling procedures and PHAGIO® therapy as the sole mouthwash prescribed for the next two weeks, three times per day.

FIGURE 1. Case 1: 28-year-old patient with severe hemophilia A and spontaneous gum bleeding


Explanations: A. Hematoma and dental Plaques; B. Severe bleeding episode from gum tissue; C. Results after two weeks of treatment with PHAGIO therapy.

## CASE 2

The 36-year-old patient with Hemophilia B (Factor IX Deficiency) admits to generalized periodontitis characterized by significant recession of both soft and hard


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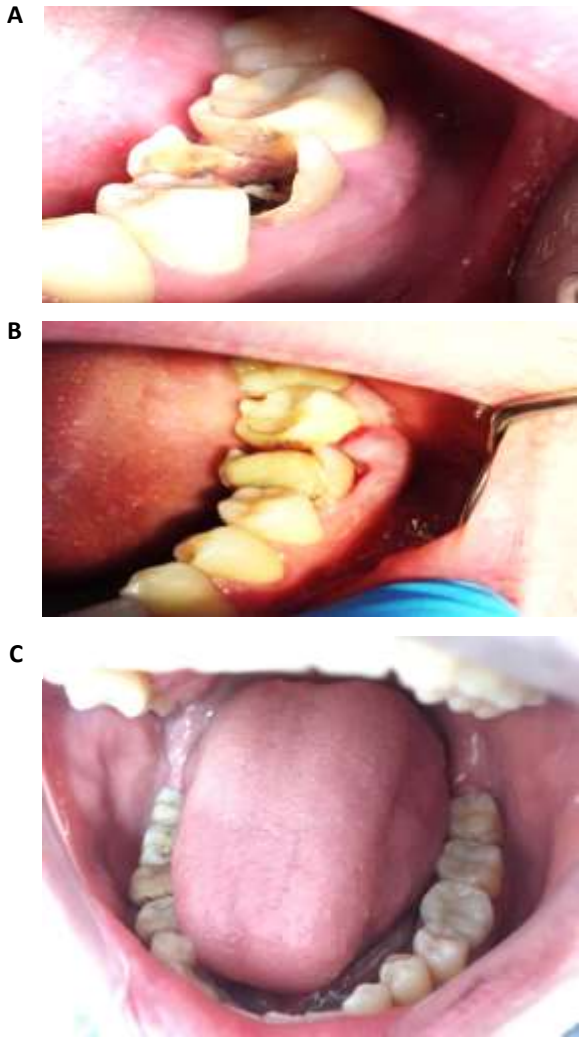
tissues. At age 36, a bleeding episode occurred in the vicinity of tooth area 36, accompanied by a very thin subgingival hematoma. Despite the patient's use of antihemophilic factor concentrates, bleeding symptoms did not improve.

A bacteriological sample was obtained from the oral cavity to assess phage resistance. After oral cavity examination and completion of a periodontal map, plaque removal was performed using scaling procedures (Fig.2 and Fig.3). PHAGIO therapy, administered as the sole mouthwash, was prescribed for the next two weeks, with a frequency of three times per day.

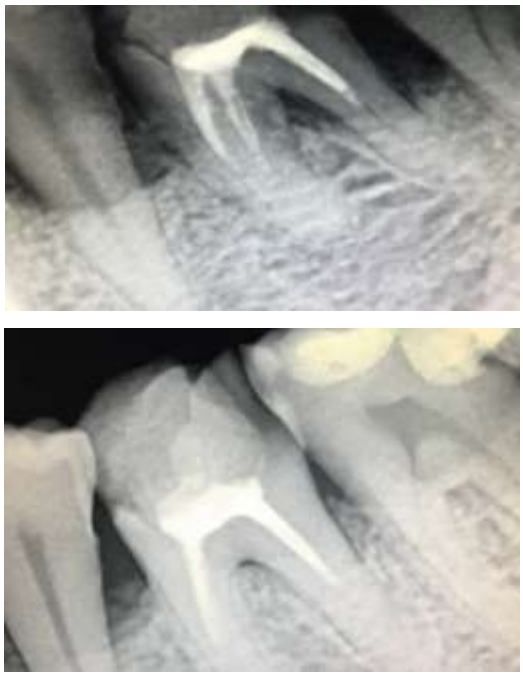
FIGURE 2. Case 2: 36-year-old patient with Hemophilia B (Factor IX Deficiency) and generalized periodontitis




Explanations: A. Bleeding and hematoma at tooth area; B. Bleeding episode is stopped, and tooth restoration was done; C. Full restoration of the tooth healthy gum tissue.

Figure 3 represents radiological images of the alveolar bone condition before and after restoration and PHAGIO therapy.

FIGURE 3. Case 2: Radiologic findings before and after treatment of a 36-year-old patient with Hemophilia B (Factor IX Deficiency) and generalized periodontitis




Explanations: A. Alveolar bone resorption before treatment; B. Bone regeneration after four months.

## CASE 3

The 19-year-old patient with Hemophilia A (Factor VIII Deficiency) with gingivitis experienced independent bleeding episodes as well as bleeding during tooth brushing. Additionally, the patient is noted to be a heavy smoker.

Clinical examination revealed swollen gum tissue, bleeding upon dental probing, halitosis, and plaque accumulation.

The treatment plan involved dental scaling without phage therapy (Fig.4 and Fig.5).

FIGURE 4. Case 3: 36-year-old patient with Hemophilia A (Factor VIII Deficiency) with gingivitis before treatment

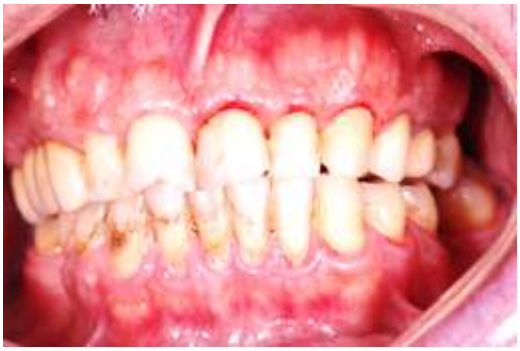


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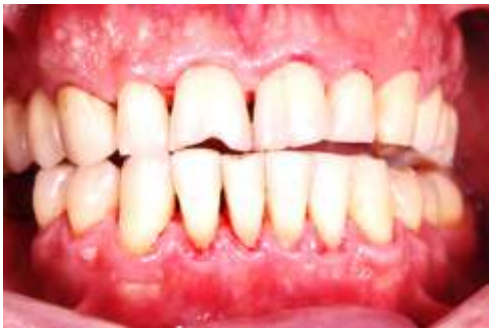
FIGURE 5. Case 3: 36-year-old patient with Hemophilia A (Factor VIII Deficiency) with gingivitis two weeks of follow-up after treatment (plaques are removed, but the bleeding is still present)



## DISCUSSION

Phage therapy, while promising, remains relatively understudied in dentistry, with limited research conducted to assess its effectiveness.[9,10] Periodontal diseases are associated with various aerobic and anaerobic pathogens. Variations in bacteriophage communities between periodontal health and disease suggest the potential development of therapies based on these communities.[11] However, phage therapy in patients with bleeding disorders has not been explored, and no publications are available on this topic. This novel treatment approach could offer a non-invasive method for managing periodontal diseases and other odontogenic or non-odontogenic inflammatory conditions.

Currently, there are over 300 registered patients with bleeding disorders in Georgia. To ensure the credibility of this study, a larger cohort of patients should be recruited, including individuals with hemophilia A and B and those with von Willebrand disease. Additionally, the follow-up period for patients should be extended to allow for comprehensive data collection and analysis.

This study utilized PHAGIO as the sole phage therapy medication, targeting a limited spectrum of bacteria, including Streptococcus, Staphylococcus, E. coli, Pseudomonas aeruginosa, and Proteus. However, other specific pathological bacteria such as Fusobacterium spp., Bacteroides fragilis, Porphyromonas spp., and Prevotella intermedia are common anaerobic pathogens implicated in periodontal disease.[12,13] Therefore, a comprehensive study involving active collaboration among hematologists, dentists, and bacteriologists is essential for advancing phage therapy in dentistry.

Oral cavity examination after four weeks of treatment revealed that in three patients of group 1, bleeding from the gum tissue had ceased entirely, with a reduction in gum tissue swelling. One patient exhibited partial improvement in bleeding episodes. Subsequent bacteriological testing revealed a significant decrease in pathogenic bacteria within the oral cavity.

In patients of group 2, oral cavity examinations revealed a decrease in bleeding; however, bleeding episodes persisted, transitioning from severe to moderate. Independent bleeding episodes were still observed.

## CONCLUSIONS

Based on the case study, using bacteriophages as an adjunctive treatment approach for oral cavity diseases demonstrated favorable outcomes, improving bleeding episodes among hemophilia patients diagnosed with gingivitis and periodontitis.

## AUTHOR AFFILIATION

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